This document was developed by NIEHS/NTP staff to facilitate internal and external review of a proposed research program prior to designing and conducting toxicology studies. The purpose of the research concept document is to outline the general elements of a research program that would address the specific public health concerns that prompted the nomination of the substance or issue for study. It may also encompass substance-specific studies that address larger public health issues or topics in toxicology. Additional information about the nomination, review, and selection of substances for study by the NTP is provided at ***Nominations to the NTP Testing Program*** (*http://ntp.niehs.nih.gov/go/nom*). A draft version of this research concept was reviewed by the NTP Board of Scientific Counselors at a public meeting on June 11-12, 2008 (*http://ntp.niehs.nih.gov/go/9741*) and subsequently approved by the NTP Executive Committee.

NTP Research Concept: 2-Ethylhexyl *p*-Methoxycinnamate

Project Leader
Michael Wyde, Ph.D.
DIR/NTP/Toxicology Branch

Nomination Background and Rationale

2-Ethylhexyl p-methoxycinnamate (EHMC) was nominated by the National Cancer Institute and recommended for comprehensive toxicological characterization including carcinogenicity and developmental toxicity studies, and characterization of photodecomposition products (http://ntp.niehs.nih.gov/go/32744). This nomination is based on high production volume, widespread consumer exposure as a common active ingredient in sunscreens, and reported estrogenic and reproductive effects.

EHMC is the most widely used ultraviolet (UV) filter in topically applied sunscreens. As a UV filter, it forms a protective layer on the surface of the skin and/or penetrates into the stratum corneum layer of the skin. EHMC protects against UV-induced sunburn, photoageing, immunosuppression, and skin cancer by absorbing harmful UVB radiation.

Studies with EHMC have repeatedly demonstrated weak estrogenic effects. These effects include altered fertility and reproductive performance, delayed sexual maturation, and altered reproductive organ weights in rodents. EHMC also caused slight but measurable effects in a 2-generation study in rats. However, the effects observed in the offspring in this study may have reflected maternal toxicity. EHMC seems to elicit a unique spectrum of alterations in luteinizing hormone, thyroid hormones, and lipids. No effects on reproductive hormones have been observed in humans.

Transdermal penetration studies demonstrate that only a small amount (<3%) of dermally-applied EHMC is absorbed and that systemic exposure is low. Studies demonstrate consistency between laboratory animals and humans in the penetration into and through the layers of the skin. The primary factors affecting penetration are formulation-dependent. Recently, new carrier systems like nanoparticle encapsulation and nanoemulsions have been investigated for enhancement of EHMC photostability and increased penetration into the stratum corneum compared to conventional oil/water emulsions. Additionally, the vehicle may modify the properties of stratum corneum and affect EHMC penetration.

Key Issues

Studies of percutaneous absorption indicate that <3% of the applied EHMC may be absorbed through the skin and reach systemic exposure. Much of the EHMC appears to be distributed in the stratum corneum in adults. However, concerns have been expressed about the use of this sunscreen ingredient in children where the stratum corneum is less likely to be protective.

Additionally, children may have less-developed elimination capacity with respect to expression and activity of cytochrome P450s and glucuronidation.

With increased awareness of the dangers of UV radiation, sunscreens are typically applied for protection throughout one's lifespan, leading to chronic exposures to sunscreen ingredients. As a result, these exposures may occur *in utero*. Studies on EHMC should take this exposure scenario into consideration.

Given the structure of EHMC, it is possible that metabolism may lead to the formation of 2-ethylhexanol and 2-ethylhexanoic acid, both of which are developmental toxicants. Metabolism of EHMC should be investigated to determine the potential formation of these metabolites.

Developmental studies are typically not conducted via the dermal route of exposure, but human exposure from sunscreen product use is nearly exclusively dermal. Toxicokinetic studies comparing the dermal and oral routes of exposure should be considered with consideration of 2-ethylhexanol and 2-ethylhexanoic acid formation. These studies will determine the concordance between the routes of exposure to preserve the relevance to the human exposure scenario.

Although studies with EHMC have repeatedly demonstrated estrogenic effects, these effects are generally weak and occur usually at high doses. There has been some debate regarding the validity of both the design of the assays performed and the use of these studies for risk assessment. These endocrine-related alterations and the controversy surrounding the effects indicate that further investigation and clarification of the reproductive effects of this potentially endocrine active compound is warranted.

Proposed Approach

Conduct comparative dermal and oral toxicokinetic (TK) studies incorporating elements of ADME to evaluate differential distribution and metabolism of EHMC between the routes of exposure. In addition to determining the potential formation of 2-ethylhexanol and 2-ethylhexanoic acid, these studies will establish the concordance between the dermal and oral routes of exposure. These issues are critical since *in utero* studies are typically not conducted via the dermal route of exposure, but the human exposure is nearly exclusively dermal.

Conduct studies to determine the photodecomposition products of EHMC.

Following the completion of TK studies, dermal or oral subacute, subchronic, and chronic studies will be conducted in rats and mice to characterize the toxicity and carcinogenicity of EHMC. The route of exposure will be determined based on the results of the initial toxicokinetic studies. To address both the issue that human exposure to sunscreens occurs generally throughout life and concerns for exposures in children, the exposure scenarios for these studies should include *in utero* exposures. Additionally, these studies should include the determination of pertinent serum hormones, including male and female sex hormones and thyroid hormone levels, since previous studies have demonstrated the potential for effects on the endocrine system.

To further clarify and definitively determine the potential for EHMC to alter fertility and reproductive development, a robust multigenerational study will be conducted in the rat incorporating estrogen-sensitive end points. The study should be over a wide dose range and utilize an increased number of pups selected to be retained to adulthood for examination. A study with this type of design, conducted by the NTP on DEHP, has indicated a significantly increased ability to detect reproductive tract effects in the F_1 and F_2 generations at lower dose levels compared to the conventional multigeneration design (NTP, 2001).

Significance and Expected Outcome

EHMC is the most widely used UVB filter ingredient in sunscreens in the United States. Although no specific exposure information is available, practical knowledge tells us that the use of sunscreens for protection from UV radiation is widespread and exposure is chronic. It is anticipated that information from these studies will serve to increase the scientific base on which regulatory agencies such as the FDA make their interpretations of the potential toxicological events associated with exposure to sunscreens that contain EHMC.

References

National Toxicology Program. (2005) Final Report on Diethylhexylphthalate Multigenerational reproductive assessment by continuous breeding when administered to Sprague-Dawley rats in the diet. NTP Study Number RACB98004. NTIS # PB2004-104000. Abstract available at http://ntp.niehs.nih.gov/go/15182.

December 2008